Basics

Hormones are *chemical signaling substances.* They are synthesized in specialized cells that are often associated to form *endocrine glands.* Hormones are released into the *blood* and transported with the blood to their *effector organs.* In the organs, the hormones carry out physiological and biochemical regulatory functions. In contrast to endocrine hormones, **tissue hormones** are only active in the immediate vicinity of the cells that secrete them.

The distinctions between hormones and other signaling substances (mediators, neurotransmitters, and growth factors) are fluid. **Mediators** is the term used for signaling substances that do not derive from special hormone-forming cells, but are form by many cell types. They have hormone-like effects in their immediate surroundings. *Histamine* (see p. 352) and *prostaglandins* (see p. 390) are important examples of these substances. **Neurohormones** and **neurotransmitters** are signaling substances that are produced and released by nerve cells (see p. 348). **Growth factors** and **cytokines** mainly promote cell proliferation and cell differentiation (see p. 392).

A. Hormones: overview ●

The animal organism contains more than 100 hormones and hormone-like substances, which can be classified either according to their structure or according to their function. In chemical terms, most hormones are *amino acid derivatives, peptides* or *proteins,* or *steroids.* Hormones regulate the following processes:

- **Growth and differentiation of cells, tissues, and organs**
  These processes include cell proliferation, embryonic development, and sexual differentiation—i. e., processes that require a prolonged time period and involve proteins de novo synthesis. For this reason, mainly steroid hormones which function via transcription regulation are active in this field (see p. 244).
- **Metabolic pathways**
  Metabolic regulation requires rapidly acting mechanisms. Many of the hormones involved therefore regulate *interconversion* of enzymes (see p. 120). The main processes subject to hormonal regulation are the uptake and degradation of storage substances (glycogen, fat), metabolic pathways for biosynthesis and degradation of central metabolites (glucose, fatty acids, etc.), and the supply of metabolic energy.
- **Digestive processes**
  Digestive processes are usually regulated by locally acting peptides (paracrine; see p. 372), but mediators, biogenic amines, and neuropeptides are also involved (see p. 270).
- **Maintenance of ion concentrations (homeostasis)**
  Concentrations of Na^+, K^+, and Cl^- in body fluids, and the physiological variables dependent on these (e. g. blood pressure), are subject to strict regulation. The principal site of action of the hormones involved is the kidneys, where hormones increase or reduce the resorption of ions and recovery of water (see pp. 326–331). The concentrations of Ca^{2+} and phosphate, which form the mineral substance of bone and teeth, are also precisely regulated.

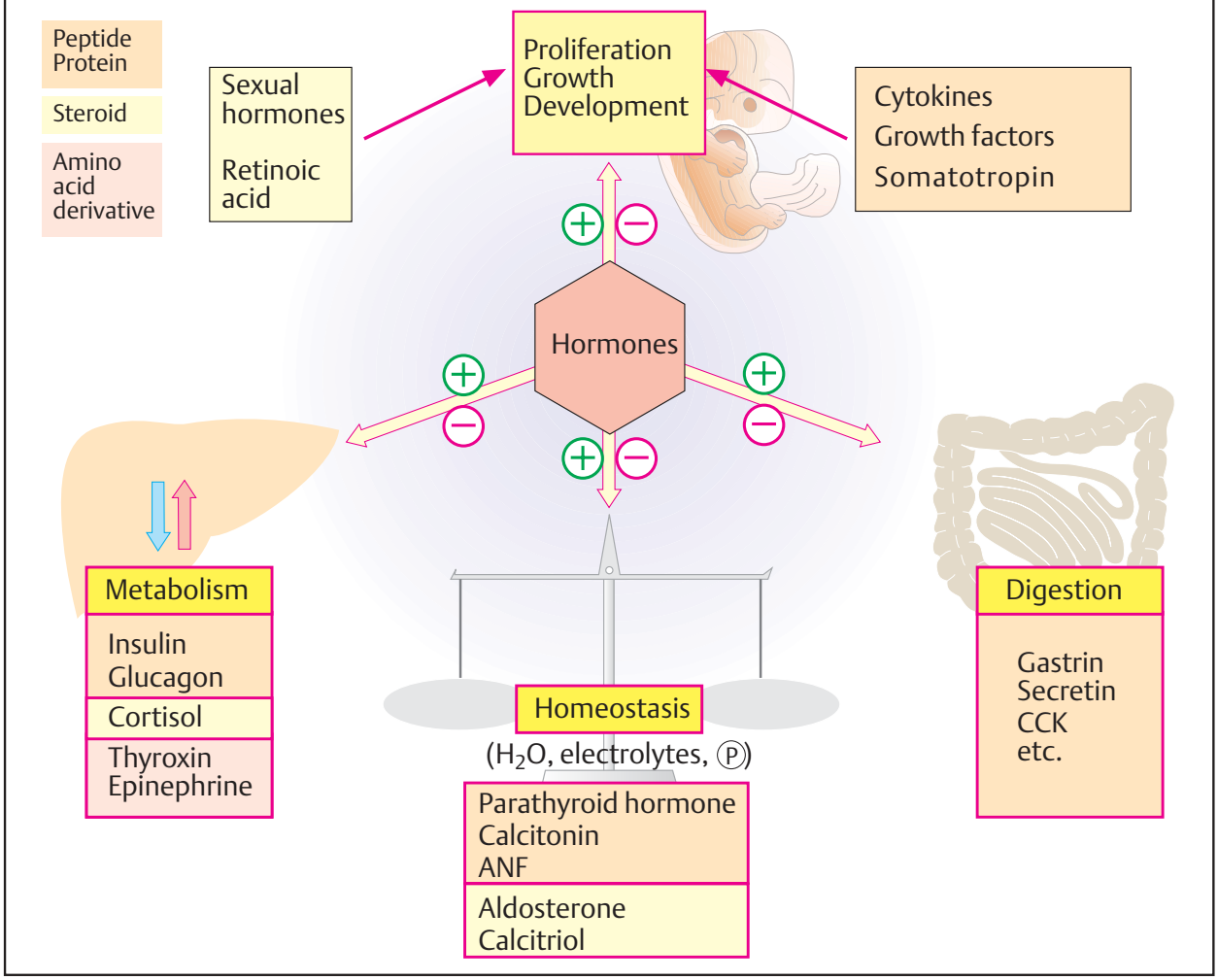
Many hormones influence the above processes only indirectly by regulating the synthesis and release of other hormones (*hormonal hierarchy;* see p. 372).

B. Hormonal regulation system ●

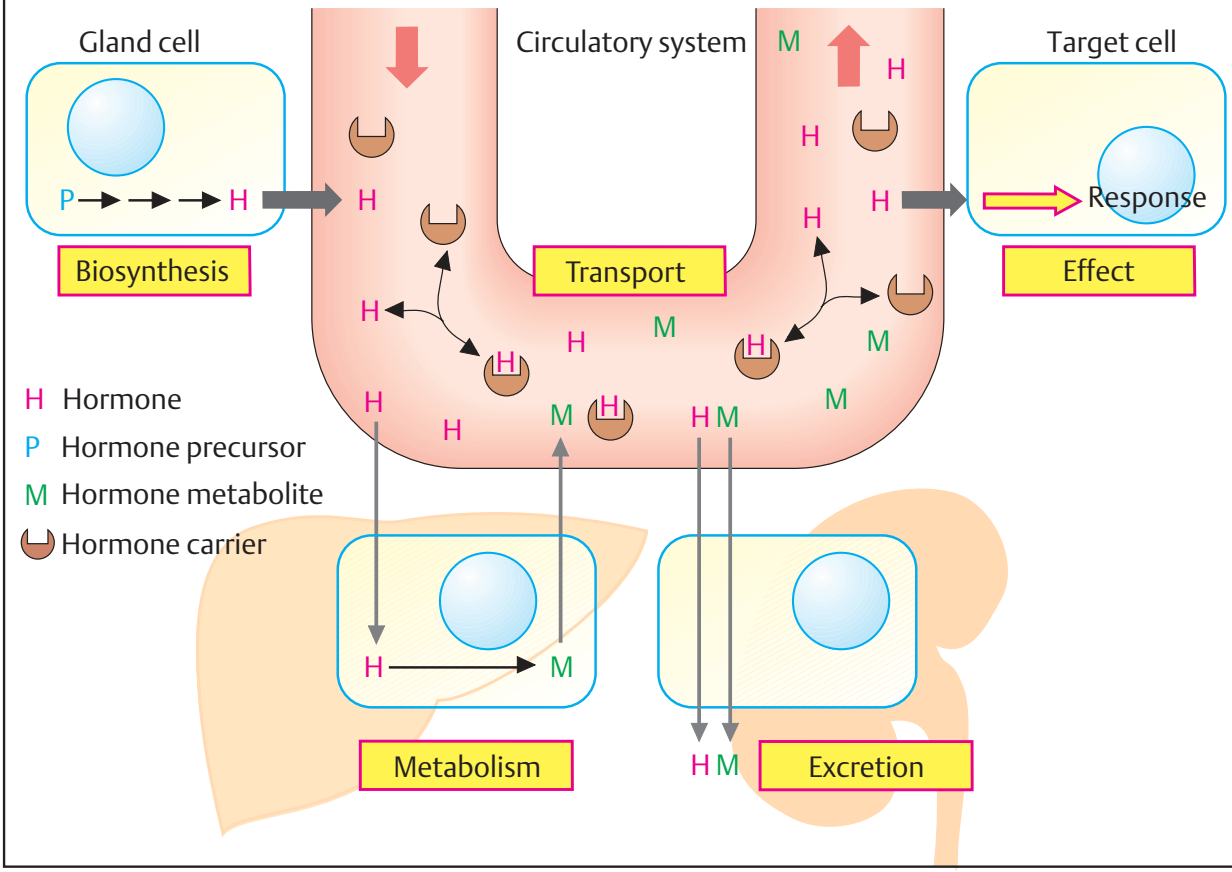
Each hormone is the center of a hormonal regulation system. Specialized glandular cells synthesize the hormone from precursors, store it in many cases, and release it into the bloodstream when needed (**biosynthesis**). For **transport**, the poorly water-soluble lipophilic hormones are bound to plasma proteins known as hormone carriers. To stop the effects of the hormone again, it is inactivated by enzymatic reactions, most of which take place in the liver (**metabolism**). Finally, the hormone and its metabolites are expelled via the excretory system, usually in the kidney (**excretion**). All of these processes affect the concentration of the hormone and thus contribute to regulation of the hormonal signal.

In the effector organs, target cells receive the hormone's message. These cells have hormone receptors for the purpose, which bind the hormone. Binding of a hormone passes information to the cell and triggers a response (**effect**).

A. Hormones: overview



A. Hormonal regulation system



Plasma levels and hormone hierarchy

A. Endocrine, paracrine, and autocrine hormone effects ◑

Hormones transfer signals by migrating from their site of synthesis to their site of action. They are usually transported in the blood. In this case, they are said to have an **endocrine effect** (**1**; example: *insulin*). By contrast, *tissue hormones,* the target cells for which are in the immediate vicinity of the glandular cells that produce them, are said to have a **paracrine effect** (**2**; example: *gastrointestinal tract hormones*). When signal substances also pass effects back to the cells that synthesize them, they are said to have an **autocrine effect** (**3**; example: *prostaglandins*). Autocrine effects are often found in tumor cells (see p. 400), which stimulate their own proliferation in this way.

Insulin, which is formed in the B cells of the pancreas, has both endocrine and paracrine effects. As a hormone with endocrine effects, it regulates glucose and fat metabolism. Via a paracrine mechanism, it inhibits the synthesis and release of *glucagon* from the neighboring A cells.

B. Dynamics of the plasma level ◑

Hormones circulate as signaling substances in the blood at very low concentrations (10^{-12} to between 10^{-7} mol L^{-1}). These values change periodically in rhythms that depend on the time of day, month, or year, or on physiological cycles.

The first example shows the **circadian** rhythm of the cortisol level. As an activator of gluconeogenesis (see p. 158), cortisol is mainly released in the early morning, when the liver's glycogen stores are declining. During the day, the plasma cortisol level declines.

Many hormones are released into the blood in a spasmodic and irregular manner. In this case, their concentrations change in an **episodic** or **pulsatile** fashion. This applies, for instance, to luteinizing hormone (LH, lutropin).

Concentrations of other hormones are **event-regulated**. For example, the body responds to increased blood sugar levels after meals by releasing *insulin.* Regulation of hormone synthesis, release, and degradation allows the blood concentrations of hormones to be precisely adjusted. This is based either on simple feedback control or on hierarchically structured regulatory systems.

C. Closed-loop feedback control ◑

The biosynthesis and release of *insulin* by the pancreatic B cells (see p. 160) is stimulated by high blood glucose levels (> 5 mM). The insulin released then stimulates increased uptake and utilization of glucose by the cells of the muscle and adipose tissues. As a result, the blood glucose level falls back to its normal value, and further release of insulin stops.

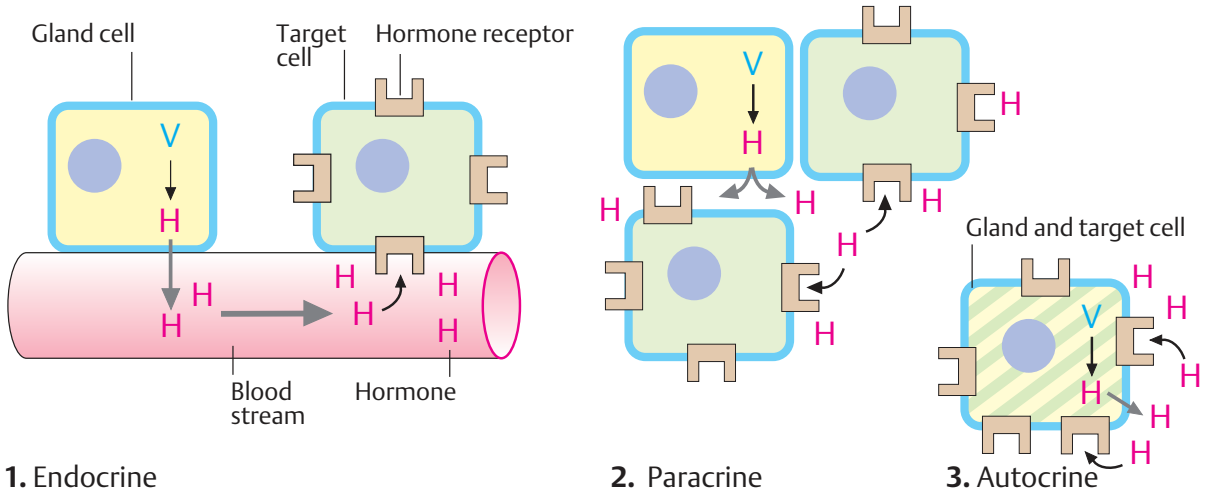
D. Hormone hierarchy ◑

Hormone systems are often linked to each another, giving rise in some cases to a hierarchy of higher-order and lower-order hormones. A particularly important example is the *pituitary–hypothalamic axis,* which is controlled by the central nervous system (CNS).

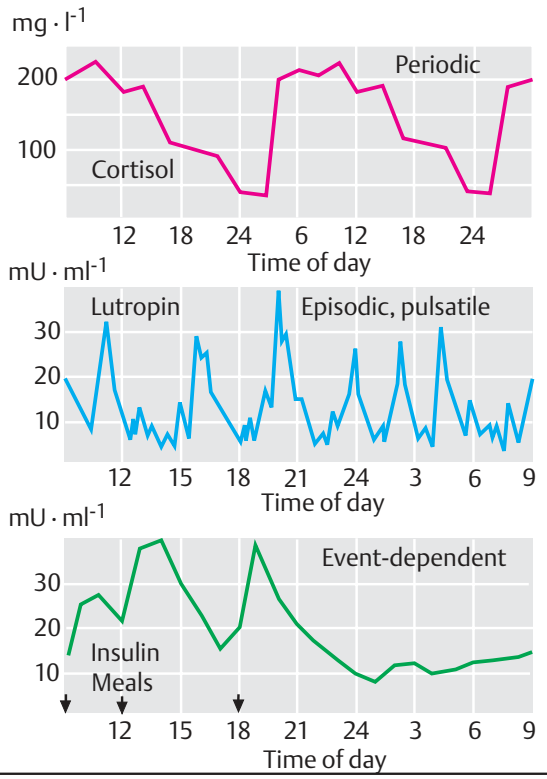
Nerve cells in the hypothalamus react to stimulatory or inhibitory signals from the CNS by releasing activating or inhibiting factors, which are known as **liberins** (*"releasing hormones"*) and **statins** (*"inhibiting hormones"*). These neurohormones reach the adenohypophysis by short routes through the bloodstream. In the adenohypophysis, they stimulate (liberins) or inhibit (statins) the biosynthesis and release of tropines. **Tropines** (*glandotropic hormones*) in turn stimulate peripheral glands to synthesize glandular hormones. Finally, the **glandular hormone** acts on its target cells in the organism. In addition, it passes effects back to the higher-order hormone systems. This (usually negative) feedback influences the concentrations of the higher-order hormones, creating a feedback loop.

Many steroid hormones are regulated by this type of axis—e.g., thyroxin, cortisol, estradiol, progesterone, and testosterone. In the case of the glucocorticoids, the hypothalamus releases corticotropin-releasing hormone (CRH or corticoliberin, a peptide consisting of 41 amino acids), which in turn releases corticotropin (ACTH, 39 AAs) in the pituitary gland. Corticotropin stimulates synthesis and release of the glandular steroid hormone cortisol in the adrenal cortex.

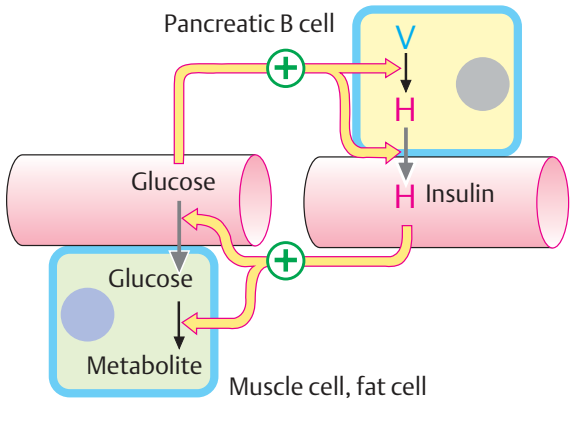
A. Endocrine, paracrine and autocrine hormone effects



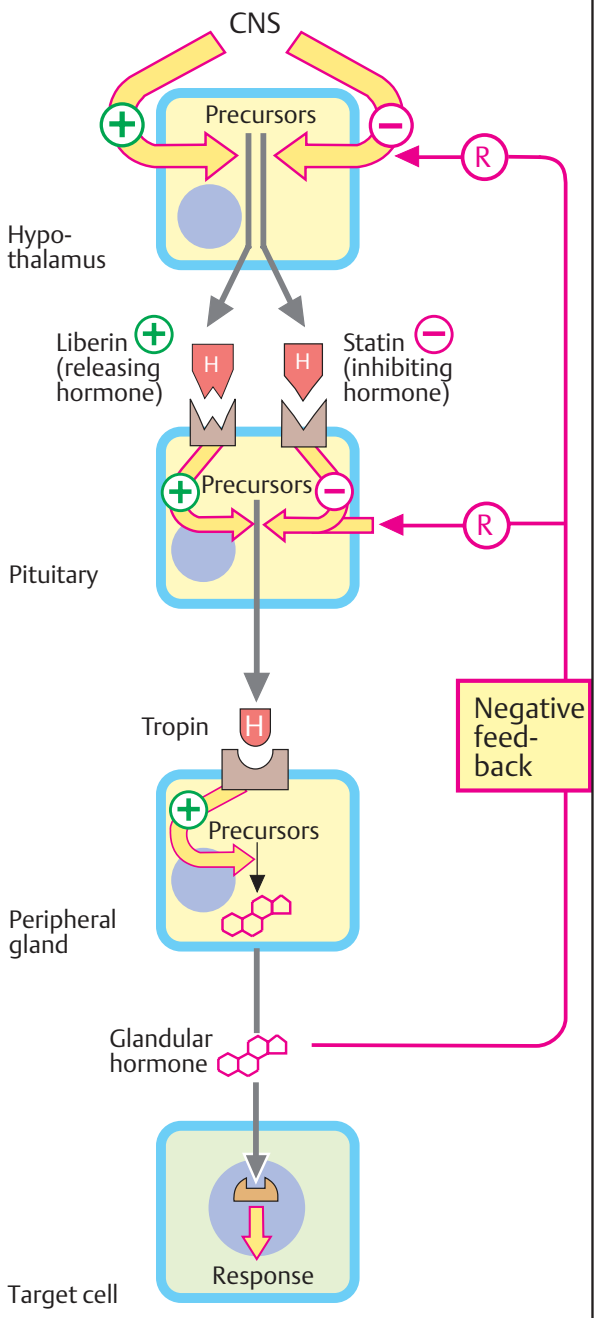
B. Plasma level dynamics



C. Regulatory circuit



D. Hormone hierarchy



Lipophilic hormones

Classifying hormones into hydrophilic and lipophilic molecules indicates the chemical properties of the two groups of hormones and also reflects differences in their mode of action (see p. 120).

A. Lipophilic hormones ◑

Lipophilic hormones, which include *steroid hormones, iodothyronines,* and *retinoic acid,* are relatively small molecules (300–800 Da) that are poorly soluble in aqueous media. With the exception of the iodothyronines, they are not stored by hormone-forming cells, but are released immediately after being synthesized. During transport in the blood, they are bound to specific carriers. Via intracellular receptors, they mainly act on transcription (see p. 358). Other effects of steroid hormones—e. g., on the immune system—are not based on transcriptional control. Their details have not yet been explained.

Steroid hormones

The most important steroid hormones in vertebrates are listed on p. 57. *Calcitriol* (vitamin D hormone) is also included in this group, although it has a modified steroid structure. The most important steroid hormone in invertebrates is *ecdysone*.

Progesterone is a female sexual steroid belonging to the progestin *(gestagen)* family. It is synthesized in the corpus luteum of the ovaries. The blood level of progesterone varies with the menstrual cycle. The hormone prepares the uterus for a possible pregnancy. Following fertilization, the placenta also starts to synthesize progesterone in order to maintain the pregnant state. The development of the mammary glands is also stimulated by progesterone.

Estradiol is the most important of the *estrogens.* Like progesterone, it is synthesized by the ovaries and, during pregnancy, by the placenta as well. Estradiol controls the menstrual cycle. It promotes proliferation of the uterine mucosa, and is also responsible for the development of the female secondary sexual characteristics (breast, fat distribution, etc.).

Testosterone is the most important of the male sexual steroids (*androgens*). It is synthesized in the Leydig intersitial cells of the testes, and controls the development and functioning of the male gonads. It also determines secondary sexual characteristics in men (muscles, hair, etc.).

Cortisol, the most important *glucocorticoid,* is synthesized by the adrenal cortex. It is involved in regulating protein and carbohydrate metabolism by promoting protein degradation and the conversion of amino acids into glucose. As a result, the blood glucose level rises (see p. 152). Synthetic glucocorticoids (e. g., dexamethasone) are used in drugs due to their anti-inflammatory and immunosuppressant effects.

Aldosterone, a *mineralocorticoid,* is also synthesized in the adrenal gland. In the kidneys, it promotes Na^+ resorption by inducing Na^+/K^+ ATPase and Na^+ channels (see p. 328). At the same time, it leads to increased K^+ excretion. In this way, aldosterone indirectly increases blood pressure.

Calcitriol is a derivative of vitamin D (see p. 364). On exposure to ultraviolet light, a precursor of the hormone can also arise in the skin. Calcitriol itself is synthesized in the kidneys (see p. 330). Calcitriol promotes the resorption of calcium in the intestine and increases the Ca^{2+} level in the blood.

Iodothyronines

The thyroid hormone **thyroxine** (tetraiodothyronine, T_4) and its active form **triiodothyronine** (T_3) are derived from the amino acid *tyrosine*. The iodine atoms at positions 3 and 5 of the two phenol rings are characteristic of them. Post-translational synthesis of thyroxine takes place in the thyroid gland from tyrosine residues of the protein *thyroglobulin,* from which it is proteolytically cleaved before being released. Iodothyronines are the only organic molecules in the animal organism that contain iodine. They increase the basal metabolic rate, partly by regulating mitochondrial ATP synthesis. In addition, they promote embryonic development.

A. Lipophilic hormones

Hormone	Site of formation	Sites of action	Actions
Progesterone	Ovaries	Uterus: Prepares uterus for pregnancy; Promotes implantation of fertilized egg	Maintenance of pregnancy ↑ Development of mammary glands ↑
Estradiol	Ovaries	Uterus and other organs: Stimulates proliferation of endometrium	Menstrual cycle Bone development ↑ Development of secondary female sex characteristics e.g., fat distribution, breasts, body hair ↑
Testosterone	Testes	Causes: Sexual differentiation to male phenotype; Formation of ejaculate; Spermatogenesis	Development of secondary male sex characteristics e.g., skeleton, muscles, body hair ↑ Protein synthesis ↑
Cortisol	Adrenal glands (cortex)	Proteins ⇄ Amino acids → Glucose	Proteolysis ↑ Protein synthesis ↓ Gluconeogenese ↑ Blut-Glucose ↑ Activity of the immune system ↓
Aldosterone	Adrenal glands (cortex)	Kidneys: $3Na^{\oplus}$, $2K^{\oplus}$; ATP → ADP+P_i	$Na^{\oplus}$ retention ↑ $K^{\oplus}$ excretion ↑ Blood pressure ↑
Calcitriol	Kidneys	Gut; Bones ⇄ $Ca^{2\oplus}$	$Ca^{2\oplus}$- and phosphate resorption ↑ $Ca^{2\oplus}$ metabolism of bones ↑
Thyroxine	Thyroid gland	Embryo; Intermediary metabolism: O_2, H_2O, S, CO_2, ADP+P_i, ATP, Heat	Fetal development, growth, and maturation ↑ Basal metabolic rate ↑ Heat generation ↑ O_2 consumption ↑

Metabolism of steroid hormones

A. Biosynthesis of steroid hormones ○

All steroid hormones are synthesized from **cholesterol.** The gonane core of cholesterol consists of 19 carbon atoms in four rings (A–D). The D ring carries a side chain of eight C atoms (see p. 54).

The cholesterol required for biosynthesis of the steroid hormones is obtained from various sources. It is either taken up as a constituent of LDL lipoproteins (see p. 278) into the hormone-synthesizing glandular cells, or synthesized by glandular cells themselves from acetyl-CoA (see p. 172). Excess cholesterol is stored in the form of fatty acid esters in lipid droplets. Hydrolysis allows rapid mobilization of the cholesterol from this reserve again.

Biosynthetic pathways. Only an overview of the synthesis pathways that lead to the individual hormones is shown here. Further details are given on p. 410.

Among the reactions involved, hydroxylations (H) are particularly numerous. These are catalyzed by specific *monooxygenases* ("hydroxylases") of the cytochrome P450 family (see p. 318). In addition, there are NADPH-dependent and $NADP^+$-dependent *hydrogenations* (Y) and *dehydrogenations* (D), as well as *cleavage* and *isomerization reactions* (S, I). The estrogens have a special place among the steroid hormones, as they are the only ones that contain an aromatic A ring. When this is formed, catalyzed by *aromatase,* the angular methyl group (C-19) is lost.

Pregnenolone is an important intermediate in the biosynthesis of most steroid hormones. It is identical to cholesterol with the exception of a shortened and oxidized side chain. Pregnenolone is produced in three steps by hydroxylation and cleavage in the side chain. Subsequent dehydrogenation of the hydroxyl group at C-3 (b) and shifting of the double bond from C-5 to C-4 results in the gestagen **progesterone**.

With the exception of calcitriol, all steroid hormones are derived from progesterone. Hydroxylations of progesterone at C atoms 17, 21, and 11 lead to the glucocorticoid **cortisol**. Hydroxylation at C-17 is omitted during synthesis of the mineralocorticoid **aldosterone.** Instead, the angular methyl group (C-18) is oxidized to the aldehyde group. During synthesis of the androgen **testosterone** from progesterone, the side chain is completely removed. Aromatization of the A ring, as mentioned above, finally leads to **estradiol**.

On the way to **calcitriol** (vitamin D hormone; see p. 342), another double bond in the B ring of cholesterol is first introduced. Under the influence of UV light on the skin, the B ring is then photochemically cleaved, and the secosteroid *cholecalciferol* arises (vitamin D_3; see p. 364). Two Cyt P450-dependent hydroxylations in the liver and kidneys produce the active vitamin D hormone (see p. 330).

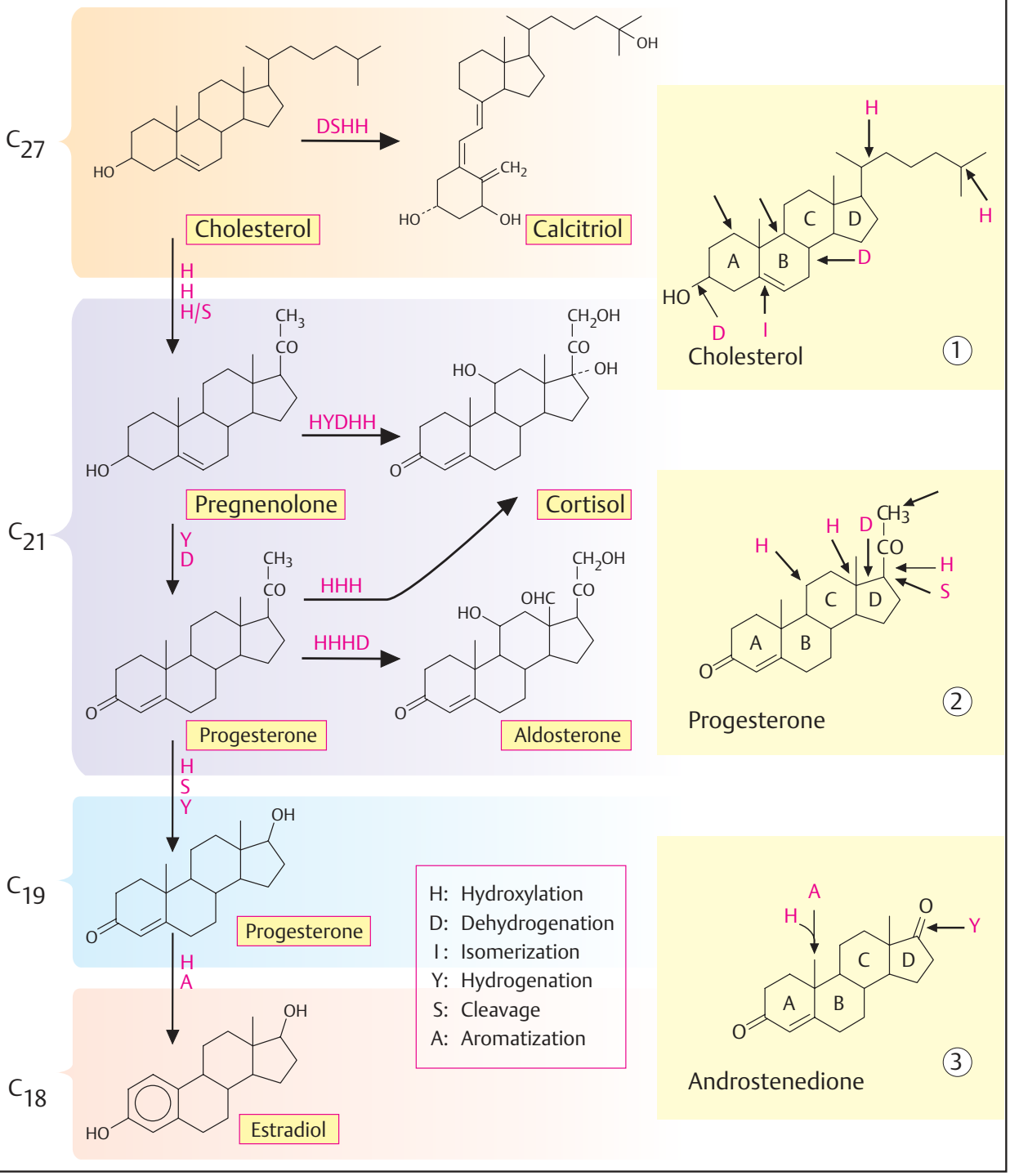
B. Inactivation of steroid hormones ○

The steroid hormones are mainly inactivated in the liver, where they are either reduced or further hydroxylated and then conjugated with *glucuronic acid* or *sulfate* for excretion (see p. 316). The *reduction reactions* attack oxo groups and the double bond in ring A. A combination of several inactivation reactions gives rise to many different steroid metabolites that have lost most of their hormonal activity. Finally, they are excreted with the *urine* and also partly via the *bile*. Evidence of steroids and steroid metabolites in the urine is used to investigate the hormone metabolism.

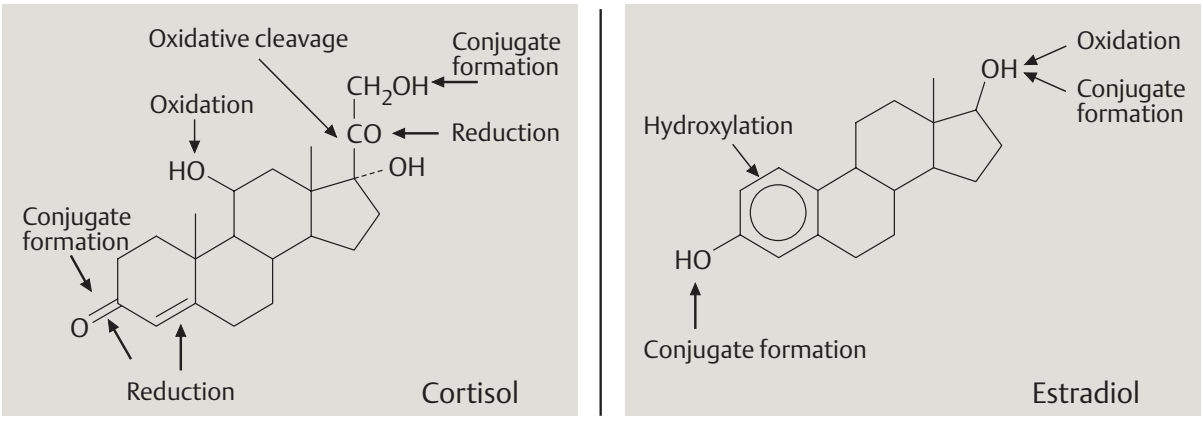
Further information

Congenital defects in the biosynthesis of steroid hormones can lead to severe developmental disturbances. In the *adrenogenital syndrome* (AGS), which is relatively common, there is usually a defect in *21-hydroxylase,* which is needed for synthesis of cortisol and aldosterone from progesterone. Reduced synthesis of this hormone leads to increased formation of testosterone, resulting in masculinization of female fetuses. With early diagnosis, this condition can be avoided by providing the mother with hormone treatment before birth.

A. Biosynthesis of steroid hormones



B. Inactivation of steroid hormones



Mechanism of action

A. Mechanism of action of lipophilic hormones ◑

Lipophilic signaling substances include the *steroid hormones, calcitriol,* the *iodothyronines* (T_3 and T_4), and *retinoic acid.* These hormones mainly act in the *nucleus* of the target cells, where they regulate gene transcription in collaboration with their receptors and with the support of additional proteins (known as coactivators and mediators; see p. 244). There are several effects of steroid hormones that are not mediated by transcription control. These alternative pathways for steroid effects have not yet been fully explained.

In the blood, there are a number of transport proteins for lipophilic hormones (see p. 276). Only the free hormone is able to penetrate the membrane and enter the cell. The hormone encounters its receptor in the nucleus (and sometimes also in the cytoplasm).

The **receptors** for lipophilic hormones are rare proteins. They occur in small numbers (10^3–10^4 molecules per cell) and show marked *specificity* and high *affinity* for the hormone (K_d = 10^{-8}–10^{-10} M). After binding to the hormone, the steroid receptors are able to bind as homodimers or heterodimers to *control elements* in the promoters of specific genes, from where they can influence the transcription of the affected genes—i. e., they act as *transcription factors.*

The illustration shows the particularly well-investigated mechanism of action for **cortisol**, which is unusual to the extent that the hormone–receptor complex already arises in the cytoplasm. The free receptor is present in the cytoplasm as a monomer in complex with the chaperone **hsp90** (see p. 232). Binding of cortisol to the complex leads to an *allosteric conformational change* in the receptor, which is then released from the hsp90 and becomes capable of DNA binding as a result of *dimerization.*

In the nucleus, the hormone–receptor complex binds to nucleotide sequences known as **hormone response elements** (HREs). These are short palindromic DNA segments that usually promote transcription as enhancer elements (see p. 244). The illustration shows the HRE for glucocorticoids (GRE; "n" stands for any nucleotide). Each hormone receptor only recognizes its "own" HRE and therefore only influences the transcription of genes containing that HRE. Recognition between the receptor and HRE is based on interaction between the amino acid residues in the DNA-binding domain (**B**) and the relevant bases in the HRE (emphasized in color in the structure illustrated).

As discussed on p. 244, the hormone receptor does not interact directly with the RNA polymerase, but rather—along with other transcription factors—with a coactivator/mediator complex that processes all of the signals and passes them on to the polymerase. In this way, hormonal effects lead within a period of minutes to hours to altered levels of mRNAs for key proteins in cellular processes ("cellular response").

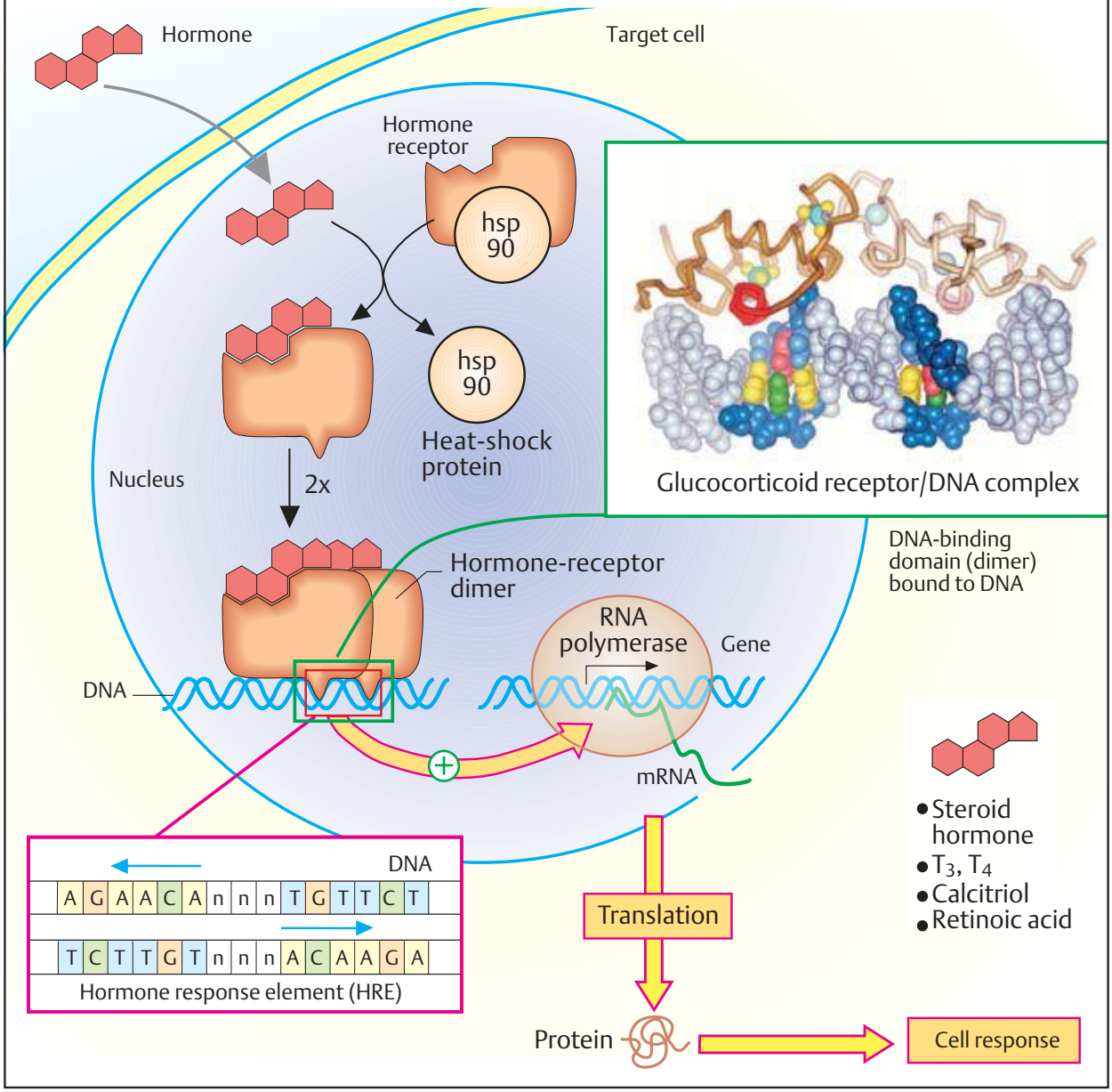
B. Steroid receptors ○

The receptors for lipophilic signaling substances all belong to one *protein superfamily.* They are constructed in a modular fashion from **domains** with various lengths and functions. Starting from the N terminal, these are: the *regulatory domain,* the *DNA-binding domain,* a *nuclear localization sequence* (see p. 228), and the *hormone-binding domain* (see p. 73D).

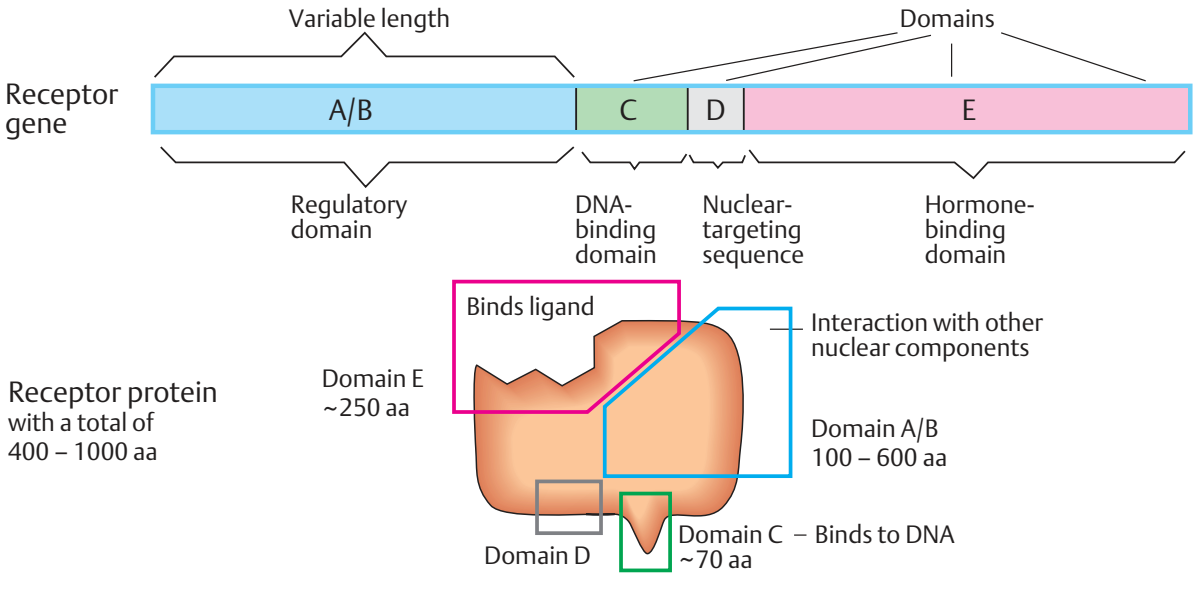
The homology among receptors is particularly great in the area of the DNA-binding domain. The proteins have cysteine-rich sequences here that coordinatively bind zinc ions (**A**, Cys shown in yellow, Zn^{2+} in light blue). These centers, known as "zinc fingers" or "**zinc clusters**," stabilize the domains and support their dimerization, but do not take part in DNA binding directly. As in other transcription factors (see p. 118), "recognition helices" are responsible for that.

In addition to the receptors mentioned in **A**, the family of steroid receptors also includes the product of the oncogene *erb*-A (see p. 398), the receptor for the environmental toxin *dioxin,* and other proteins for which a distinct hormone ligand has not been identified (known as "orphan receptors"). Several steroid receptors—e. g., the retinoic acid receptor—form functional heterodimers with orphan receptors.

A. Mechanism of action of lipophilic hormones



B. Receptors of lipophilic hormones



Hydrophilic hormones

The hydrophilic hormones are derived from amino acids, or are peptides and proteins composed of amino acids. Hormones with endocrine effects are synthesized in glandular cells and stored there in vesicles until they are released. As they are easily soluble, they do not need carrier proteins for transport in the blood. They bind on the plasma membrane of the target cells to receptors that pass the hormonal signal on (signal transduction; see p. 384). Several hormones in this group have paracrine effects—i.e., they only act in the immediate vicinity of their site of synthesis (see p. 372).

A. Signaling substances derived from amino acids ◑

Histamine, serotonin, melatonin, and the catecholamines dopa, dopamine, norepinephrine, and epinephrine are known as *"biogenic amines."* They are produced from amino acids by decarboxylation and usually act not only as hormones, but also as neurotransmitters.

Histamine, an important *mediator* (local signaling substance) and *neurotransmitter,* is mainly stored in tissue mast cells and basophilic granulocytes in the blood. It is involved in inflammatory and allergic reactions. "Histamine liberators" such as tissue hormones, type E immunoglobulins (see p. 300), and drugs can release it. Histamine acts via various types of receptor. Binding to H_1 receptors promotes contraction of smooth muscle in the bronchia, and dilates the capillary vessels and increases their permeability. Via H_2 receptors, histamine slows down the heart rate and promotes the formation of HCl in the gastric mucosa. In the brain, histamine acts as a neurotransmitter.

Epinephrine is a hormone synthesized in the adrenal glands from tyrosine (see p. 352). Its release is subject to neuronal control. This "emergency hormone" mainly acts on the blood vessels, heart, and metabolism. It constricts the blood vessels and thereby increases blood pressure (via α_1 and α_2 receptors); it increases cardiac function (via β_2 receptors); it promotes the degradation of glycogen into glucose in the liver and muscles (via β_2 receptors); and it dilates the bronchia (also via β_2 receptors).

B. Examples of peptide hormones and proteohormones ◑

Numerically the largest group of signaling substances, these arise by protein biosynthesis (see p. 382). The smallest peptide hormone, thyroliberin (362 Da), is a tripeptide. Proteohormones can reach masses of more than 20 kDa—e.g., thyrotropin (28 kDa). Similarities in the primary structures of many peptide hormones and proteohormones show that they are related to one another. They probably arose from common predecessors in the course of evolution.

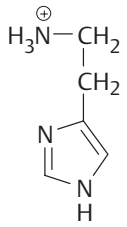
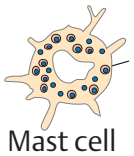
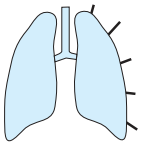
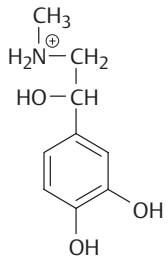
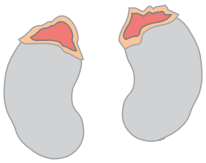
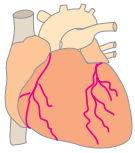
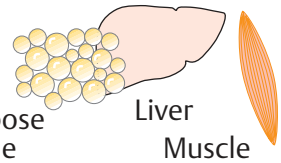
Thyroliberin (thyrotropin-releasing hormone, TRH) is one of the neurohormones of the hypothalamus (see p. 330). It stimulates pituitary gland cells to secrete thyrotropin (TSH). TRH consists of three amino acids, which are modified in characteristic ways (see p. 353).

Thyrotropin (thyroid-stimulating hormone, TSH) and the related hormones *lutropin* (luteinizing hormone, LH) and *follitropin* (follicle-stimulating hormone, FSH) originate in the adenohypophysis. They are all dimeric glycoproteins with masses of around 28 kDa. Thyrotropin stimulates the synthesis and secretion of thyroxin by the thyroid gland.

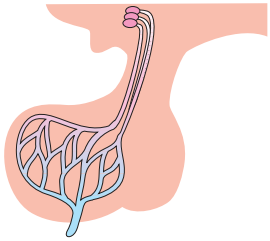
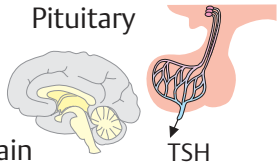
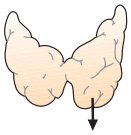
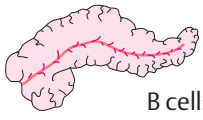
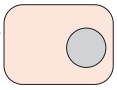
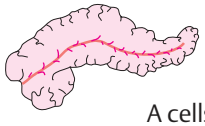
Insulin (for the structure, see p. 70) is produced and released by the B cells of the pancreas and is released when the glucose level rises. Insulin reduces the blood sugar level by promoting processes that consume glucose—e.g., glycolysis, glycogen synthesis, and conversion of glucose into fatty acids. By contrast, it inhibits gluconeogenesis and glycogen degradation. The transmission of the insulin signal in the target cells is discussed in greater detail on p. 388.

Glucagon, a peptide of 29 amino acids, is a product of the A cells of the pancreas. It is the antagonist of insulin and, like insulin, mainly influences carbohydrate and lipid metabolism. Its effects are each opposite to those of insulin. Glucagon mainly acts via the second messenger cAMP (see p. 384).

A. Signaling substances derived from amino acids

Hormone	Sites of formation	Sites of action	Actions
 Histamine	 Mast cell; Histamine stores;  Basophilic granulocyte	 Lungs;  Stomach	Width of bronchi ↓ Capillaries: width ↑ permeability ↑ Gastric acid secretion by parietal cells ↑
 Epinephrine	Adrenal glands (medulla) 	 Heart;  Adipose tissue; Liver; Muscle	Cardiac output ↑ Width of blood vessels ↓ Blood pressure ↑ Metabolism: Glycogenolysis ↑ Blood glucose ↑ Lipolysis ↑

B. Examples of peptide hormones and proteohormones

Thyroliberin (TRH) 3 AA Thyrotropin (TSH) α chain 92 AA β chain 112 AA	Hypothalamus  Adeno-hypophysis	Pituitary  Brain; TSH  Thyroid gland; Thyroxine	Thyrotropin secretion ↑ Neurotransmitter action Synthesis and secretion of thyroxine ↑
Insulin A chain 21 AA B chain 30 AA	 B cells; Pancreas	Glucose →  Glycogen ↑↓ Glucose; Proteins ↑↓ Amino acids; Fats ↑↓ Fatty acids	Glucose uptake by cells ↑ Blood glucose ↓ Storage compounds: formation ↑ degradation ↓
Glucagon 29 AA	 A cells; Pancreas	Glycogen ↓ Glucose ← Amino acids Fats ↓ Fatty acids ↓ Ketone bodies	Glycogenolysis ↑ Gluconeogenesis ↑ Blood glucose ↑ Ketone body formation ↑

Metabolism of peptide hormones

Hydrophilic hormones and other water-soluble signaling substances have a variety of biosynthetic pathways. Amino acid derivatives arise in special *metabolic pathways* (see p. 352) or through *post-translational modification* (see p. 374). Proteohormones, like all proteins, result from *translation* in the ribosome (see p. 250). Small peptide hormones and neuropeptides, most of which only consist of 3–30 amino acids, are released from precursor proteins by *proteolytic degradation*.

A. Biosynthesis ○

The illustration shows the synthesis and processing of the precursor protein **proopiomelanocortin** (POMC) as an example of the biosynthesis of small peptides with signaling functions. POMC arises in cells of the adenohypophysis, and after processing in the rER and Golgi apparatus, it supplies the opiate-like peptides *met-enkephalin* and *β-endorphin* (implying "opio-"; see p. 352), three *melanocyte-stimulating hormones* (α-, β- and γ-MSH, implying "melano-"), and the glandotropic hormone *corticotropin* (ACTH, implying "-cortin"). Additional products of POMC degradation include two *lipotropins* with catabolic effects in the adipose tissue (β- and γ-LPH).

Some of the peptides mentioned are overlapping in the POMC sequence. For example, additional cleavage of ACTH gives rise to α-MSH and corticotropin-like intermediary peptide (CLIP). Proteolytic degradation of β-LPH provides γ-LPH and β-endorphin. The latter can be further broken down to yield met-enkephalin, while γ-LPH can still give rise to β-MSH (not shown). Due to the numerous derivative products with biological activity that it has, POMC is also known as a **polyprotein**. Which end product is formed and in what amounts depends on the activity of the proteinases in the ER that catalyze the individual cleavages.

The principles underlying protein synthesis and protein maturation (see pp. 230–233) can be summed up once again using the example of POMC:

[1] As a result of *transcription* of the POMC gene and *maturation of the hnRNA,* a mature **mRNA** consisting of some 1100 nucleotides arises, which is modified at both ends (see p. 246). This mRNA codes for prepro-POMC—i.e., a POMC protein that still has a signal peptide for the ER at the N terminus (see p. 230).

[2] **Prepro-POMC** arises through *translation* in the rough endoplasmic reticulum (rER). The growing peptide chain is introduced into the ER with the help of a signal peptide.

[3] Cleavage of the signal peptide and other modifications in the ER (formation of disulfide bonds, glycosylation, phosphorylation) give rise to the mature prohormone ("**pro-POMC**").

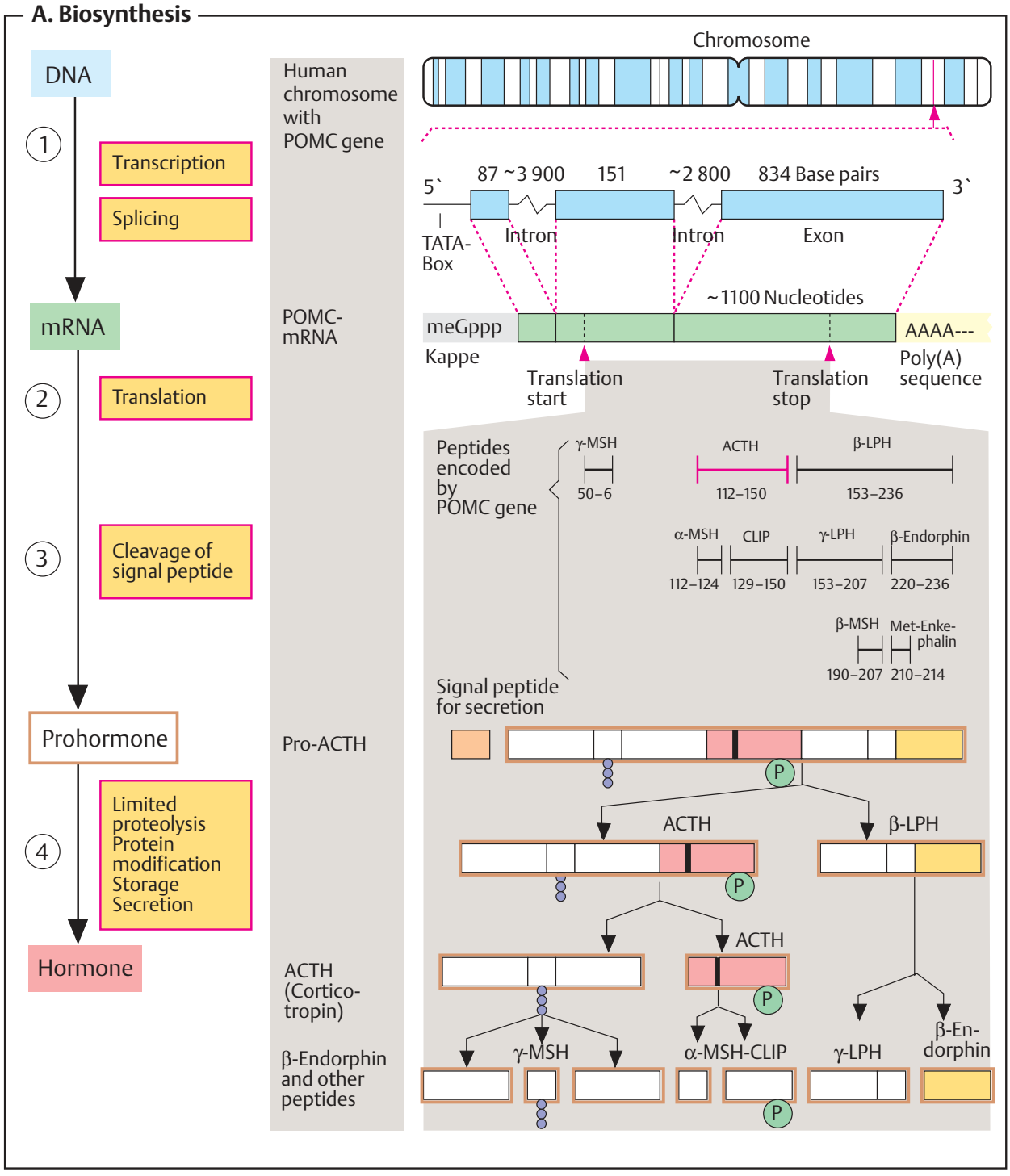
[4] The **neuropeptides** and **hormones** mentioned are now formed by *limited proteolysis* and stored in vesicles. Release from these vesicles takes place by exocytosis when needed.

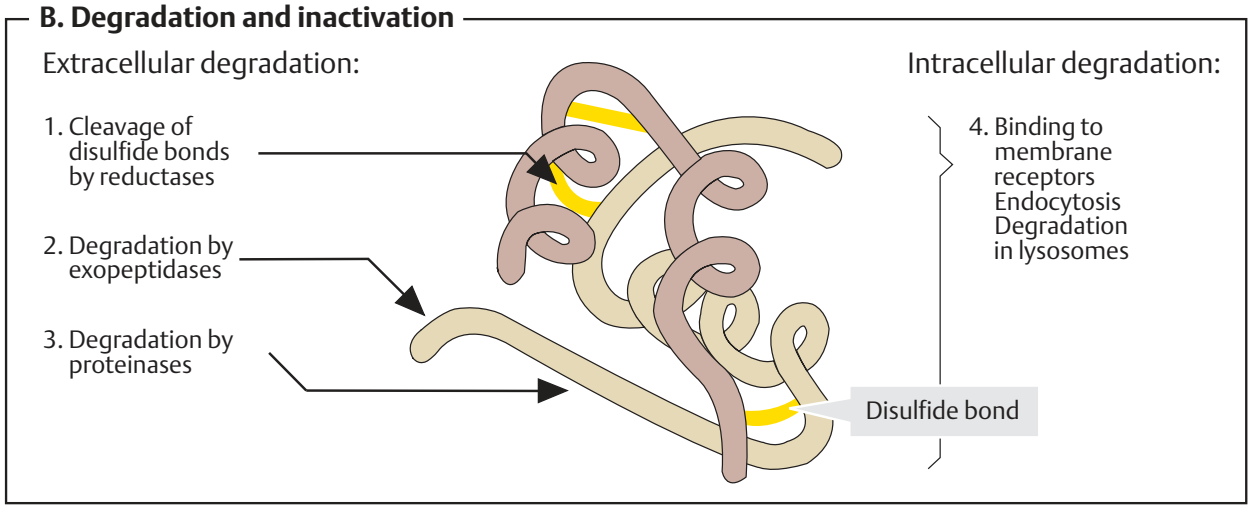
The biosynthesis of peptide hormones and proteohormones, as well as their secretion, is controlled by higher-order regulatory systems (see p. 372). Calcium ions are among the substances involved in this regulation as *second messengers;* an increase in calcium ions stimulates synthesis and secretion.

B. Degradation and inactivation ◑

Degradation of peptide hormones often starts in the blood plasma or on the vascular walls; it is particularly intensive in the kidneys.

Several peptides that contain disulfide bonds (e.g., insulin) can be inactivated by reductive *cleavage of the disulfide bonds* (**1**). Peptides and proteins are also cleaved by *peptidases,* starting from one end of the peptide by *exopeptidases* (**2**), or in the middle of it by proteinases (endopeptidases, **3**). *Proteolysis* gives rise to a variety of hormone fragments, several of which are still biologically active. Some peptide hormones and proteohormones are removed from the blood by binding to their receptors with subsequent *endocytosis* of the hormone–receptor complex (**4**). They are then broken down in the lysosomes. All of the degradation reactions lead to amino acids, which become available to the metabolism again.





Mechanisms of action

The messages transmitted by hydrophilic signaling substances (see p. 380) are sent to the interior of the cell by *membrane receptors.* These bind the hormone on the outside of the cell and trigger a new second signal on the inside by altering their conformation. In the interior of the cell, this secondary signal influences the activity of enzymes or ion channels. Via further steps, *switching of the metabolism,* changes in the *cytoskeleton,* and activation or inhibition of *transcription factors* can occur *("signal transduction")* can occur.

A. Mechanisms of action ◑

Receptors are classified into three different types according to their structure (see also p. 224):

1. 1-Helix receptors (left) are proteins that span the membrane with only one α-helix. On their inner (cytoplasmic) side, they have domains with *allosterically activatable enzyme activity.* In most cases, these are *tyrosine kinases.*

Insulins (see p. 388), *growth factors,* and *cytokines* (see p. 392), for example, act via 1-helix receptors. Binding of the signaling substance leads to activation of internal kinase activity (in some cases, dimerization of the receptor is needed for this). The activated kinase phosphorylates itself using ATP (*autophosphorylation*), and also phosphorylates tyrosine residues of other proteins (known as *receptor substrates*). Adaptor proteins that recognize the phosphotyrosine residues bind to the phosphorylated proteins (see pp. 388, 392). They pass the signal on to other protein kinases.

2. Ion channels (center). These receptors contain *ligand-gated ion channels.* Binding of the signaling substance opens the channels for ions such as Na^+, K^+, Ca^{2+}, and Cl^-. This mechanism is mainly used by *neurotransmitters* such as *acetylcholine* (nicotinic receptor; see p. 224) and *GABA* (A receptor; see p. 354).

3. 7-Helix receptors (serpentine receptors, right) represent a large group of membrane proteins that transfer the hormone or transmitter signal, with the help of *G proteins* (see below), to *effector proteins* that alter the concentrations of *ions* and *second messengers* (see **B**).

B. Signal transduction by G proteins ◑

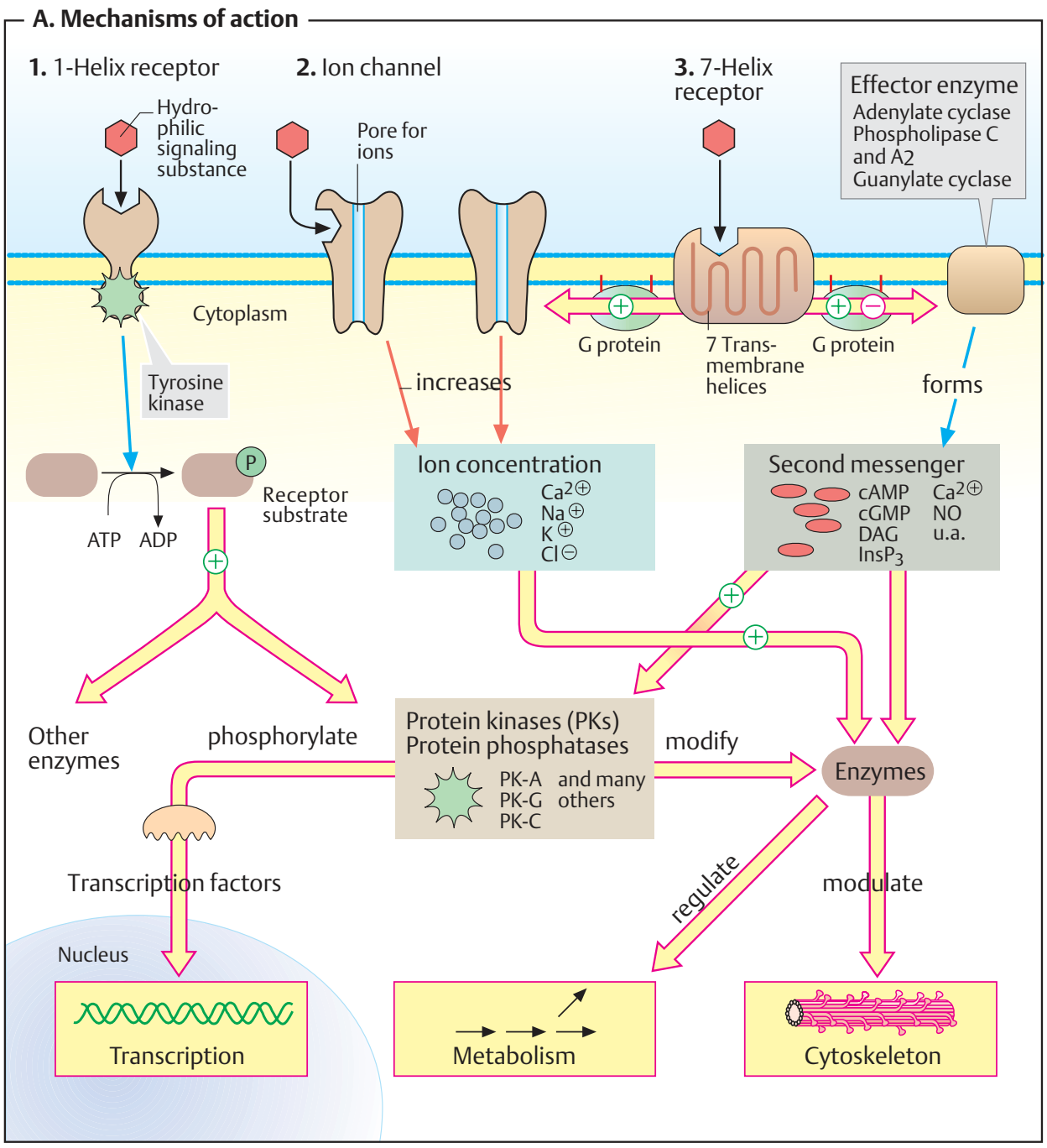
G proteins transfer signals from 7-helix receptors to effector proteins (see above). G protein are *heterotrimers* consisting of three different types of subunit (α, β, and γ; see p. 224). The α-subunit can bind GDP or GTP (hence the name "G protein") and has *GTPase activity.* Receptor-coupled G proteins are related to other GTP-binding proteins such as *Ras* (see pp. 388, 398) and *EF-Tu* (see p. 252).

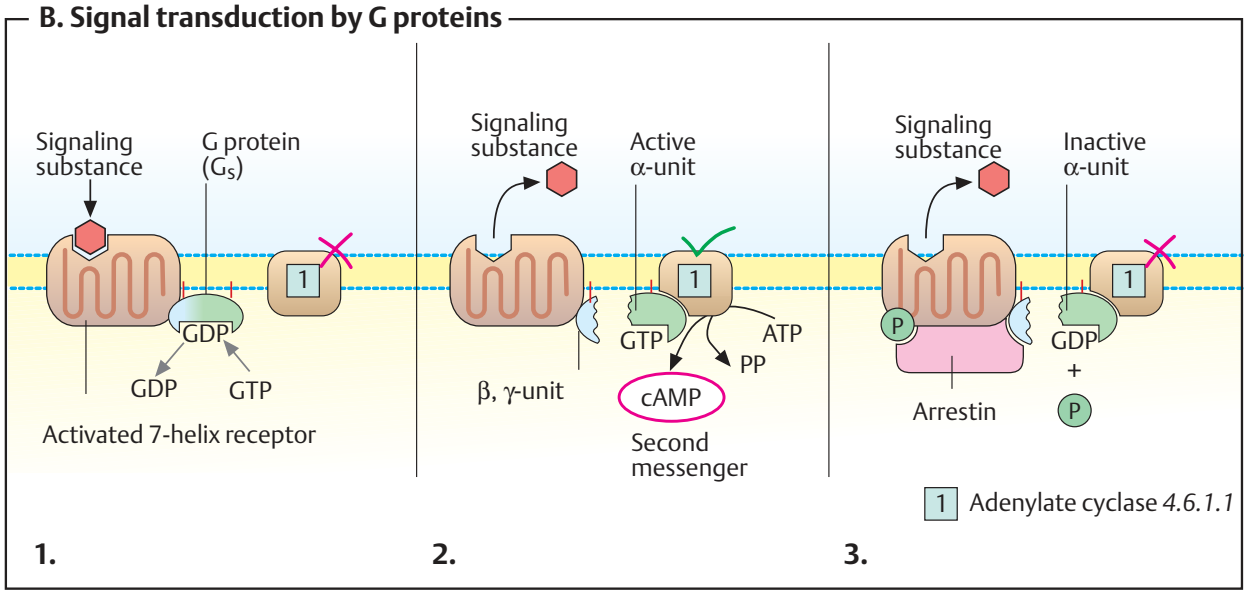
G proteins are divided into several types, depending on their effects. *Stimulatory G proteins* ($\mathbf{G_s}$) are widespread. They activate adenylate cyclases (see below) or influence ion channels. *Inhibitory G proteins* ($\mathbf{G_i}$) *inhibit* adenylate cyclase. G proteins in the G_q *family* activate another effector enzyme—phospholipase c (see p. 386).

Binding of the signaling substance to a 7-helix receptor alters the receptor conformation in such a way that the corresponding G protein can attach on the inside of the cell. This causes the α-subunit of the G protein to exchange bound GDP for GTP (**1**). The G protein then separates from the receptor and dissociates into an α-subunit and a βγ-unit. Both of these components bind to other membrane proteins and alter their activity; *ion channels* are opened or closed, and *enzymes* are activated or inactivated.

In the case of the β_2-catecholamine receptor (illustrated here), the α-subunit of the G_s protein, by binding to adenylate cyclase, leads to the synthesis of the **second messenger** cAMP. cAMP activates protein kinase A, which in turn activates or inhibits other proteins (**2**; see p. 120).

The βγ-unit of the G protein stimulates a kinase (βARK, not shown), which phosphorylates the receptor. This reduces its af nity for the hormone and leads to binding of the blocking protein *arrestin.* The internal GTPase activity of the α-subunit hydrolyzes the bound GTP to GDP within a period of seconds to minutes, and thereby terminates the action of the G protein on the adenylate cyclase (**3**).





Second messengers

Second messengers are *intracellular* chemical signals, the concentration of which is regulated by hormones, neurotransmitters, and other extracellular signals (see p. 384). They arise from easily available substrates and only have a short half-life. The most important second messengers are cAMP, cGMP, Ca^{2+}, inositol triphosphate ($InsP_3$), diacylglycerol (DAG), and nitrogen monoxide (NO).

A. Cyclic AMP ◑

Metabolism. The nucleotide **cAMP** (adenosine 3′,5′-cyclic monophosphate) is synthesized by membrane-bound *adenylate cyclases* [1] on the inside of the plasma membrane. The adenylate cyclases are a family of enzymes that cyclize ATP to cAMP by cleaving diphosphate (PP_i). The degradation of cAMP to AMP is catalyzed by *phosphodiesterases* [2], which are inhibited by *methylxanthines* such as caffeine, for example. By contrast, *insulin* activates the esterase and thereby reduces the cAMP level (see p. 388).

Adenylate cyclase activity is regulated by *G proteins* (G_s and G_i), which in turn are controlled by extracellular signals via *7-helix receptors* (see p. 384). Ca^{2+}-calmodulin (see below) also activates specific adenylate cyclases.

Action. cAMP is an allosteric effector of *protein kinase A* (PK-A, [3]). In the inactive state, PK-A is a heterotetramer (C_2R_2), the catalytic subunits of which (C) are blocked by regulatory units (R; autoinhibition). When cAMP binds to the regulatory units, the C units separate from the R units and become enzymatically active. Active PK-A phosphorylates serine and threonine residues of more than 100 different proteins, enzymes, and transcription factors. In addition to cAMP, **cGMP** also acts as a second messenger. It is involved in sight (see p. 358) and in the signal transduction of NO (see p. 388).

B. Inositol 1,4,5-trisphosphate and diacylglycerol ◑

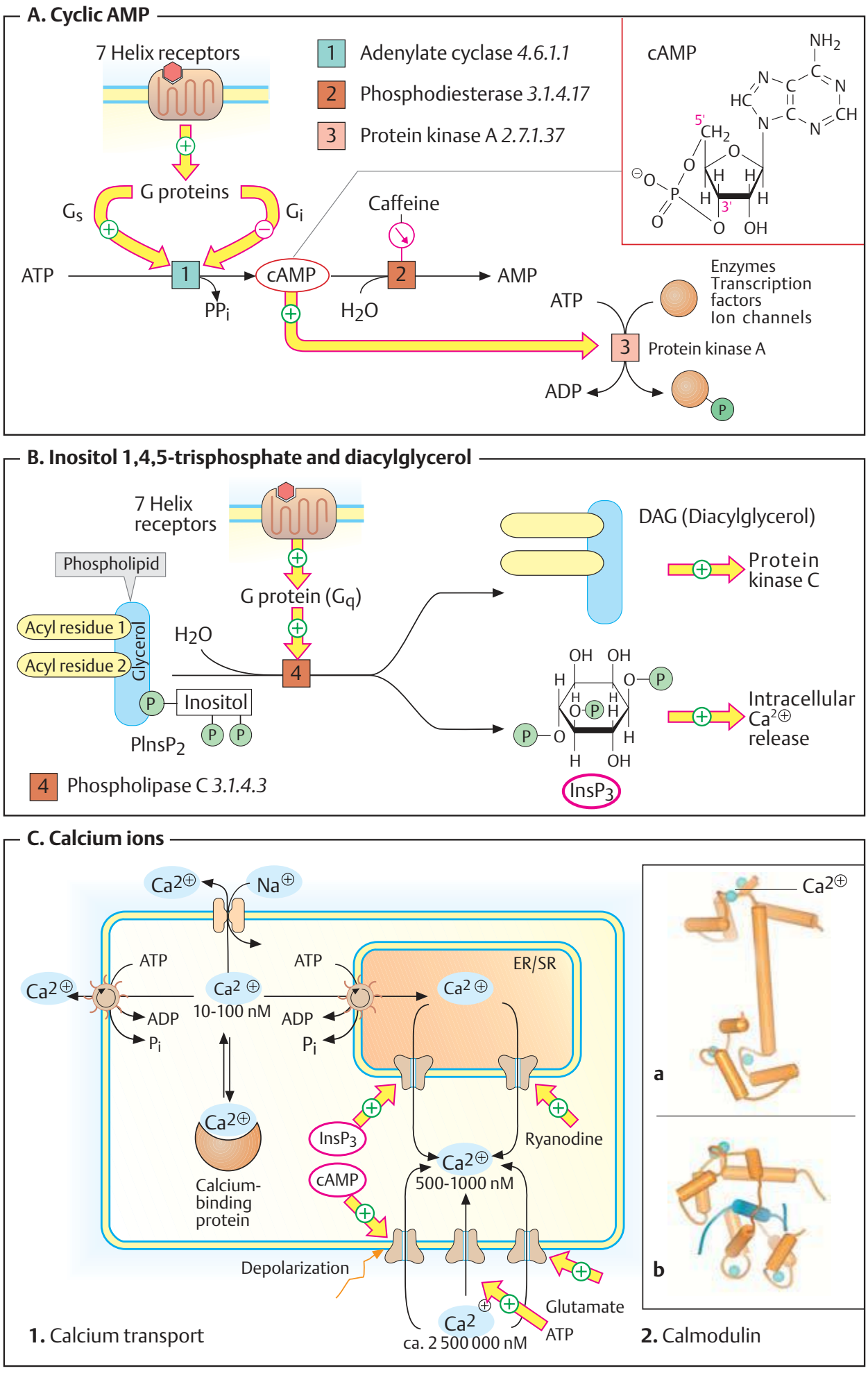
Type G_q G proteins activate *phospholipase C* [4]. This enzyme creates two second messengers from the double-phosphorylated membrane phospholipid *phosphatidylinositol bisphosphate* ($PInsP_2$), i.e., inositol 1,4,5-trisphosphate (**InsP3**), which is soluble, and diacylglycerol (**DAG**). $InsP_3$ migrates to the endoplasmic reticulum (ER), where it opens Ca^{2+} channels that allow Ca^{2+} to flow into the cytoplasm (see **C**). By contrast, DAG, which is lipophilic, remains in the membrane, where it activates type C *protein kinases*, which phosphorylate proteins in the presence of Ca^{2+} ions and thereby pass the signal on.

C. Calcium ions ◑

Calcium level. Ca^{2+} (see p. 342) is a signaling substance. The concentration of Ca^{2+} ions in the cytoplasm is normally very low (10–100 nM), as it is kept down by ATP-driven Ca^{2+} pumps and Na^+/Ca^{2+} exchangers. In addition, many proteins in the cytoplasm and organelles bind calcium and thus act as Ca^{2+} buffers.

Specific signals (e.g., an action potential or second messenger such as $InsP_3$ or cAMP) can trigger a sudden increase in the cytoplasmic Ca^{2+} level to 500–1000 nM by opening Ca^{2+} channels in the plasma membrane or in the membranes of the *endoplasmic* or *sarcoplasmic reticulum*. *Ryanodine,* a plant substance, acts in this way on a specific channel in the ER. In the cytoplasm, the Ca^{2+} level always only rises very briefly (Ca^{2+} "spikes"), as prolonged high concentrations in the cytoplasm have cytotoxic effects.

Calcium effects. The biochemical effects of Ca^{2+} in the cytoplasm are mediated by special Ca^{2+}-binding proteins (*"calcium sensors"*). These include the *annexins, calmodulin,* and *troponin C* in muscle (see p. 334). **Calmodulin** is a relatively small protein (17 kDa) that occurs in all animal cells. Binding of four Ca^{2+} ions (light blue) converts it into a *regulatory element.* Via a dramatic conformational change (cf. 2a and 2b), Ca^{2+}-calmodulin enters into interaction with other proteins and modulates their properties. Using this mechanism, Ca^{2+} ions regulate the activity of enzymes, ion pumps, and components of the cytoskeleton.



Signal cascades

The signal transduction pathways that mediate the effects of the metabolic hormone **insulin** are of particular medical interest (see **A**). The mediator **nitrogen monoxide** (NO) is also clinically important, as it regulates vascular caliber and thus the body's perfusion with blood (see **B**).

A. Insulin: signal transduction ○

The diverse effects of insulin (see p. 160) are mediated by protein kinases that mutually activate each other in the form of enzyme cascades. At the end of this chain there are kinases that influence gene transcription in the nucleus by phosphorylating target proteins, or promote the uptake of glucose and its conversion into glycogen. The signal transduction pathways involved have not yet been fully explained. They are presented here in a simplified form.

The **insulin receptor** (top) is a dimer with subunits that have activatable tyrosine kinase domains in the interior of the cell (see p. 224). Binding of the hormone increases the tyrosine kinase activity of the receptor, which then phosphorylates itself and other proteins (**receptor substrates**) at various tyrosine residues. **Adaptor proteins**, which conduct the signal further, bind to the phosphotyrosine residues.

The effects of insulin on transcription are shown on the left of the illustration. Adaptor proteins **Grb-2** and **SOS** ("son of sevenless") bind to the phosphorylated **IRS** (insulin-receptor substrate) and activate the G protein **Ras** (named after its gene, the oncogene *ras*; see p. 398). Ras activates the protein kinase **Raf** (another oncogene product). Raf sets in motion a phosphorylation cascade that leads via the kinases **MEK** and **ERK** (also known as MAPK, "mitogen-activated protein kinase") to the phosphorylation of transcription factors in the nucleus.

Some of the effects of insulin on the **carbohydrate metabolism** (right part of the illustration) are possible without protein synthesis. In addition to Grb-2, another dimeric adaptor protein can also bind to phosphorylated IRS. This adaptor protein thereby acquires *phosphatidylinositol-3-kinase* activity (**PI_3K**) and, in the membrane, phosphorylates phospholipids from the phosphatidylinositol group (see p. 50) at position 3. Protein kinase **PDK-1** binds to these reaction products, becoming activated itself and in turn activating protein kinase B (**PK-B**).

This has several effects. In a manner not yet fully understood, PK-B leads to the fusion with the plasma membrane of vesicles that contain the glucose transporter Glut-4. This results in inclusion of Glut-4 in the membrane and thus to increased glucose uptake into the muscles and adipose tissue (see p. 160). In addition, PK-B inhibits glycogen synthase kinase 3 (**GSK-3**) by phosphorylation. As GSK-3 in turn inhibits glycogen synthase by phosphorylation (see p. 120), its inhibition by PK-B leads to *increased* glycogen synthesis. Protein phosphatase-1 (**PP-1**) converts glycogen synthase into its active form by dephosphorylation (see p. 120). PP-1 is also activated by insulin.

B. Nitrogen monoxide (NO) as a mediator ○

Nitrogen monoxide (NO) is a short-lived radical that functions as a locally acting mediator (see p. 370).

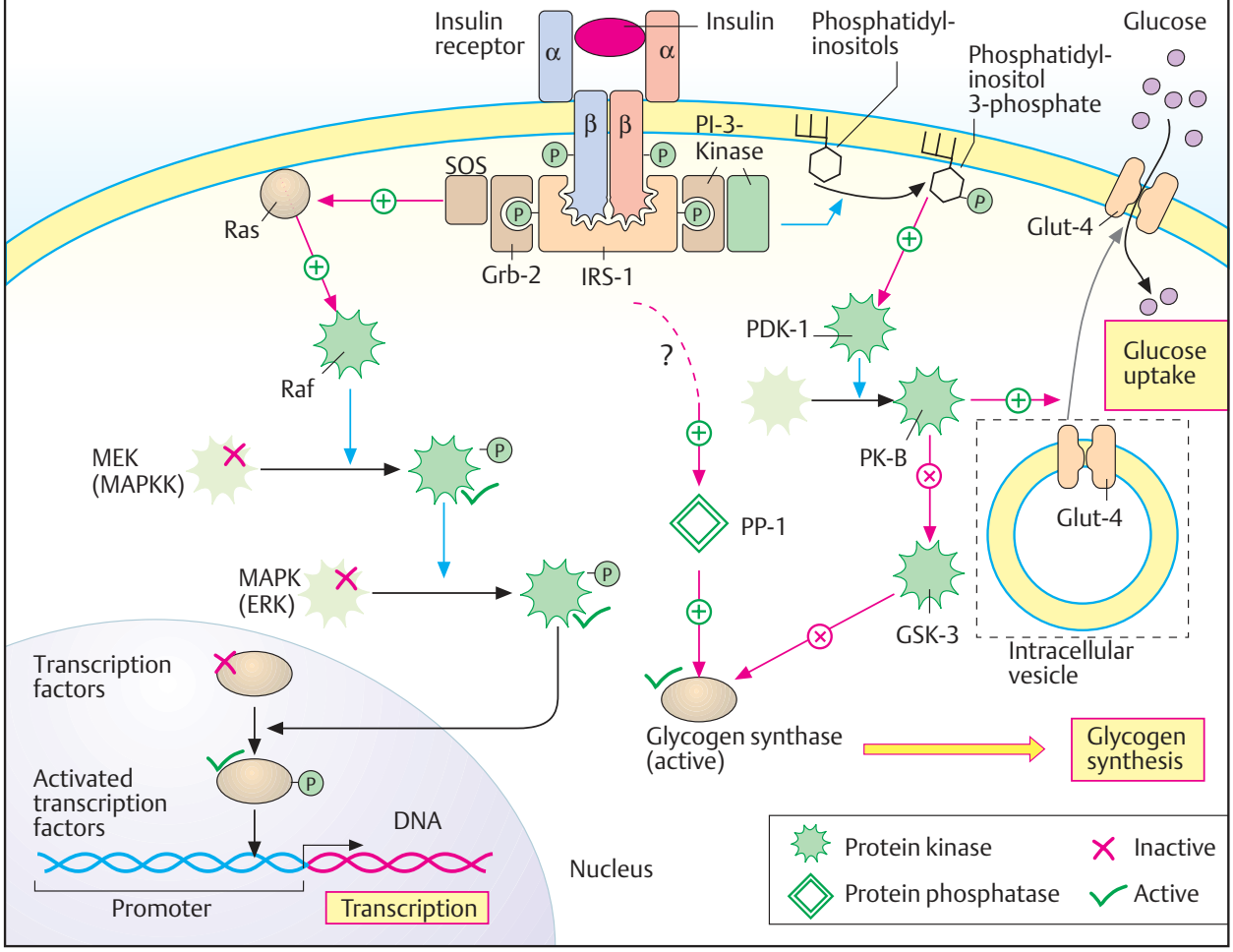
In a complex reaction, NO arises from arginine in the endothelial cells of the blood vessels [1]. The trigger for this is Ca^{2+}-calmodulin (see p. 386), which forms when there is an increase in the cytoplasmic Ca^{2+} level.

NO diffuses from the endothelium into the underlying vascular muscle cells, where it leads, as a result of activation of *guanylate cyclase* [2], to the formation of the second messenger **cGMP** (see pp. 358, 384). Finally, by activating a special protein kinase (**PK-G**), cGMP triggers relaxation of the smooth muscle and thus dilation of the vessels. The effects of atrionatriuretic peptide (**ANP**; see p. 328) in reducing blood pressure are also mediated by cGMP-induced vasodilation. In this case, cGMP is formed by the guanylate cyclase activity of the ANP receptor.

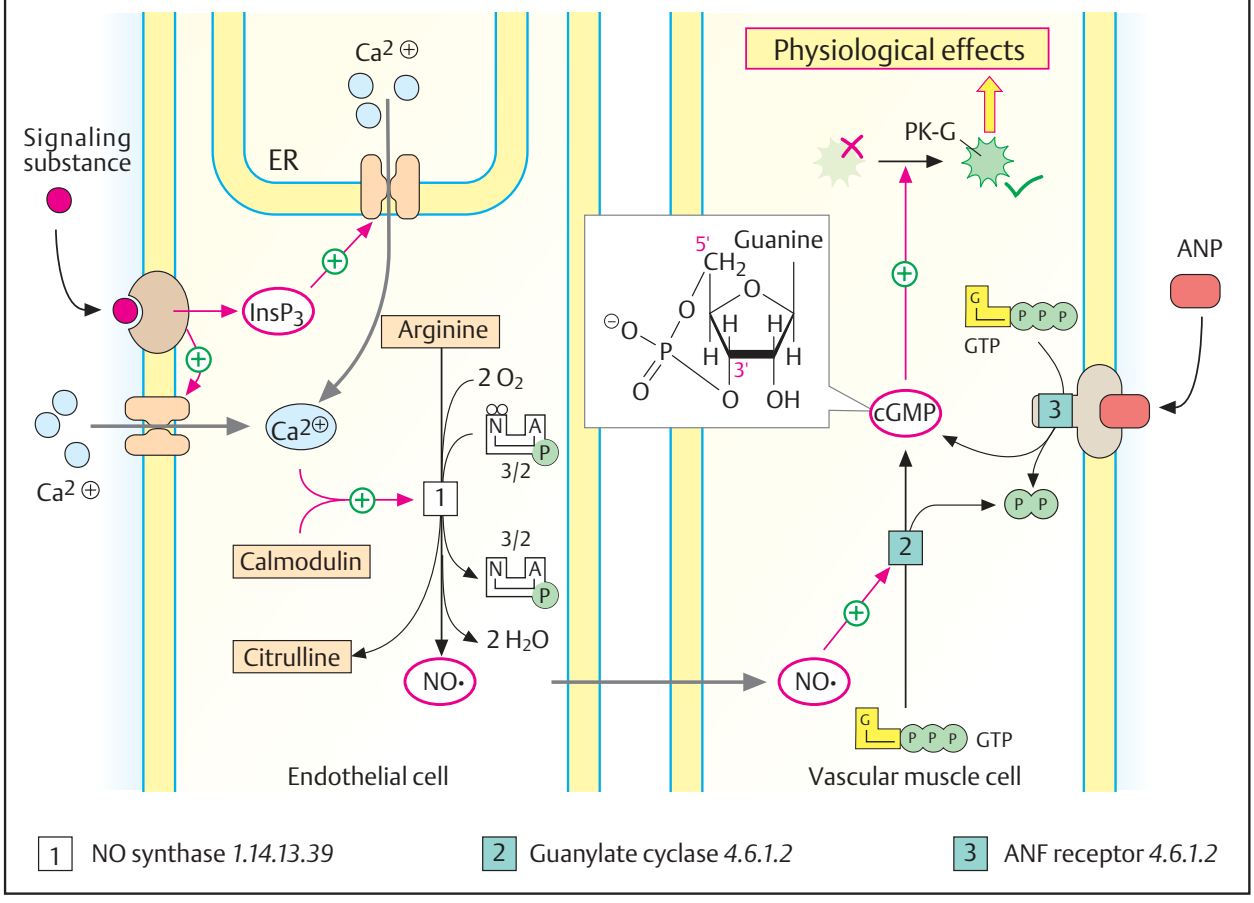
Further information

The drug *nitroglycerin* (glyceryl trinitrate), which is used in the treatment of *angina pectoris,* releases NO in the bloodstream and thereby leads to better perfusion of cardiac muscle.

A. Insulin: signal transduction



B. Nitrogen monoxide (NO) as a mediator



Eicosanoids

The eicosanoids are a group of signaling substances that arise from the C-20 fatty acid *arachidonic acid* and therefore usually contain 20 C atoms (Greek *eicosa* = 20). As mediators, they influence a large number of physiological processes (see below). Eicosanoid metabolism is therefore an important drug target. As short-lived substances, eicosanoids only act in the vicinity of their site of synthesis (paracrine effect; see p. 372).

A. Eicosanoids ○

Biosynthesis. Almost all of the body's cells form eicosanoids. Membrane phospholipids that contain the polyunsaturated fatty acid **arachidonic acid** (20:4; see p. 48) provide the starting material.

Initially, *phospholipase A_2* [1] releases the arachidonate moiety from these phospholipids. The activity of phospholipase A_2 is strictly regulated. It is activated by hormones and other signals via *G proteins*. The arachidonate released is a signaling substance itself. However, its metabolites are even more important.

Two different pathways lead from arachidonate to **prostaglandins**, **prostacyclins**, and **thromboxanes**, on the one hand, or **leukotrienes** on the other. The key enzyme for the first pathway is *prostaglandin synthase* [2]. Using up O_2, it catalyzes in a two-step reaction the cyclization of arachidonate to prostaglandin H_2, the parent substance for the prostaglandins, prostacyclins, and thromboxanes. Acetylsalicylic acid (aspirin) irreversibly acetylates a serine residue near the active center of prostaglandin synthase, so that access for substrates is blocked (see below).

As a result of the action of *lipoxygenases* [3], hydroxyfatty acids and hydroperoxyfatty acids are formed from arachidonate, from which elimination of water and various conversion reactions give rise to the leukotrienes. The formulae only show one representative from each of the various groups of eicosanoids.

Effects. Eicosanoids act via membrane receptors in the immediate vicinity of their site of synthesis, both on the synthesizing cell itself (*autocrine* action) and on neighboring cells (*paracrine* action). Many of their effects are mediated by the second messengers cAMP and cGMP.

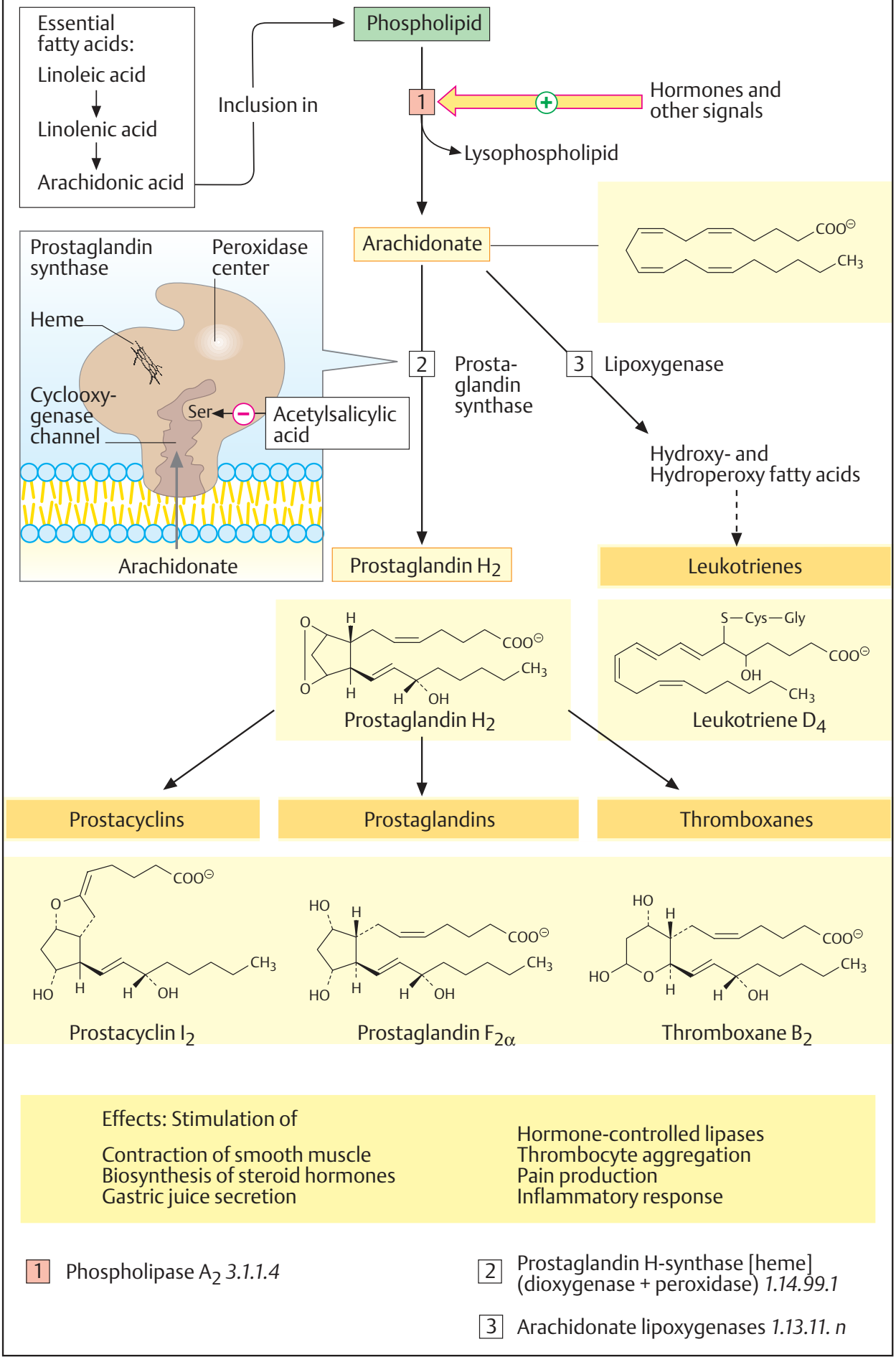
The eicosanoids have a very wide range of physiological effects. As they can stimulate or inhibit smooth-muscle contraction, depending on the substance concerned, they affect blood pressure, respiration, and intestinal and uterine activity, among other properties. In the stomach, prostaglandins inhibit HCl secretion via G_i proteins (see p. 270). At the same time, they promote mucus secretion, which protects the gastric mucosa against the acid. In addition, prostaglandins are involved in bone metabolism and in the activity of the sympathetic nervous system. In the immune system, prostaglandins are important in the inflammatory reaction. Among other things, they attract leukocytes to the site of infection. Eicosanoids are also decisively involved in the development of pain and fever. The thromboxanes promote thrombocyte aggregation and other processes involved in hemostasis (see p. 290).

Metabolism. Eicosanoids are inactivated within a period of seconds to minutes. This takes place by enzymatic reduction of double bonds and dehydrogenation of hydroxyl groups. As a result of this rapid degradation, their range is very limited.

Further information

Acetylsalicylic acid and related non-steroidal anti-inflammatory drugs (NSAIDs) selectively inhibit the *cyclooxygenase activity* of prostaglandin synthase [2] and consequently the synthesis of most eicosanoids. This explains their analgesic, antipyretic, and antirheumatic effects. Frequent side effects of NSAIDs also result from inhibition of eicosanoid synthesis. For example, they impair hemostasis because the synthesis of thromboxanes by thrombocytes is inhibited. In the stomach, NSAIDs increase HCl secretion and at the same time inhibit the formation of protective mucus. Long-term NSAID use can therefore damage the gastric mucosa.

A. Eicosanoids



Cytokines

A. Cytokines ◑

Cytokines are hormone-like *peptides* and *proteins* with signaling functions, which are synthesized and released by cells of the immune system and other cell types. Their numerous biological functions operate in three areas: they regulate the *development and homeostasis of the immune system;* they control the *hematopoietic system;* and they are involved in *non-specific defense,* influencing inflammatory processes, blood coagulation, and blood pressure. In general, cytokines regulate the growth, differentiation, and survival of cells. They are also involved in regulating apoptosis (see p. 396).

There is an extremely large number of cytokines; only the most important representatives are listed opposite. The cytokines include *interleukins* (IL), *lymphokines, monokines, chemokines, interferons* (IFN), and *colony-stimulating factors* (CSF). Via interleukins, immune cells stimulate the proliferation and activity of other immune cells (see p. 294). Interferons are used medically in the treatment of viral infections and other diseases.

Although cytokines rarely show structural homologies with each other, their effects are often very similar. The cytokines differ from *hormones* (see p. 370) only in certain respects: they are released by many different cells, rather than being secreted by defined glands, and they regulate a wider variety of target cells than the hormones.

B. Signal transduction in the cytokines ○

As peptides or proteins, the cytokines are **hydrophilic signaling substances** that act by binding to *receptors* on the cell surface (see p. 380). Binding of a cytokine to its receptor (**1**) leads via several intermediate steps (**2** –**5**) to the activation of transcription of specific genes (**6**).

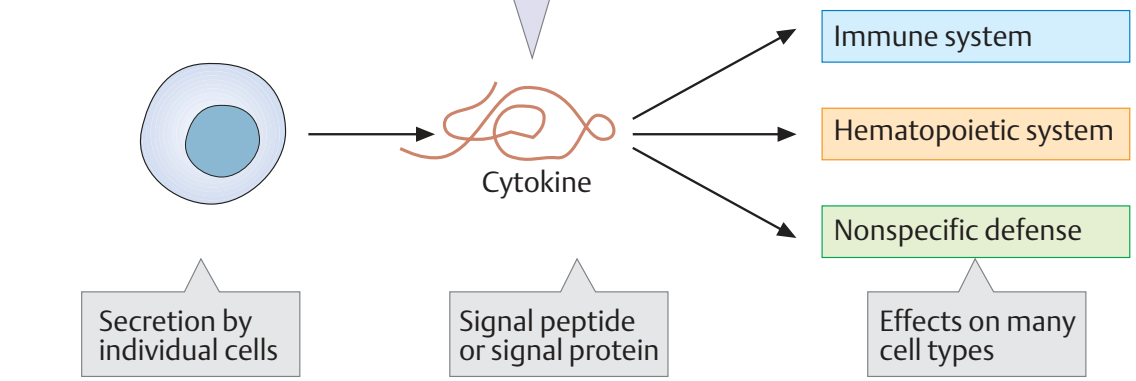
In contrast to the receptors for insulin and growth factors (see p. 388), the **cytokine receptors** (with a few exceptions) have *no* tyrosine kinase activity. After binding of cytokine (**1**), they associate with one another to form homodimers, join together with other signal transduction proteins (STPs) to form dimers, or promote dimerization of other STPs (2). Class I cytokine receptors interact with three different STPs (gp130, β_c, and γ_c). The STPs themselves do not bind cytokines, but conduct the signal to tyrosine kinases (**3**). The fact that different cytokines can activate the same STP via their receptors explains the overlapping biological activity of some cytokines.

As an example of the signal transduction pathway in cytokines, the illustration shows the way in which the **IL-6 receptor**, after binding its ligand **IL-6** (**1**), induces the dimerization of the STP **gp130** (**2**). The dimeric gp130 binds cytoplasmic *tyrosine kinases* from the Jak family ("**Janus kinases**," with two kinase centers) and activates them (**3**). The Janus kinases phosphorylate cytokine receptors, STPs, and various cytoplasmic proteins that conduct the signal further. In addition, they phosphorylate transcription factors known as **STATs** ("**s**ignal **t**ransducers and **a**ctivators of **t**ranscription"). STATs are among the proteins that have an *SH2 domain* and are able to bind phosphotyrosine residues (see p. 388). They therefore bind to cytokine receptors that have been phosphorylated by Janus kinases. When STATs are then also phosphorylated themselves (**4**), they are converted into their active form and become dimers (**5**). After transfer to the nucleus, they bind—along with auxiliary proteins as transcription factors—to the promoters of inducible genes and in this way regulate their transcription (**6**).

The activity of the cytokine receptors is terminated by *protein phosphatases,* which hydrolytically cleave the phosphotyrosine residues. Several cytokine receptors are able to lose their ligand-binding extracellular domain by proteolysis (not shown). The extracellular domain then appears in the blood, where it competes for cytokines. This reduces the effective cytokine concentration.

A. Cytokines

IL-1	Interleukin 1	G-CSF	Granulocyte colony-stimulating factor
IL-2	Interleukin 2	GM-CSF	Granulocyte/macrophage colony-stimulating factor
IL-3	Interleukin 3		
IL-4	Interleukin 4	MIF	Macrophage migration inhibitory factor
IL-5	Interleukin 5	M-CSF	Monocyte colony-stimulating factor
IL-6	Interleukin 6	TNFα	Tumor necrosis factor- α
IFN-α	Interferon α	TNFβ	Tumor necrosis factor- β
IFN-β	Interferon β		
IFN-γ	Interferon γ	and others	



B. Signal transduction in the cytokines